Diphtheria: The Present-Day Problem

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SUMMARY

The importance of diphtheria today is made evident not only by the continued frequency of its occurrence but also by its tendency to attack the older adult population. The high mortality and complication rate can be attributed in part to this shift in age incidence, as well as to delayed recognition and treatment.

THE consideration of diphtheria as a problem in this age of preventive medicine and chemotherapy may seem at first to be unusual. However, this disease not only continues to occur with significant frequency but has become more common in recent years, most particularly in the older age groups where the mortality and complications are increasingly important. The concept that diphtheria is a disease of younger children was well established in the early part of the twentieth century, when over 80 per cent of the cases occurred in children under five years of age.[5] Even as recently as 1947, it was said that about one-half the cases of diphtheria occur in children under the age of five years.[7]

A shift in the incidence of the disease toward the older age groups was stressed by Geiger in 1945.[4] This study showed an increasing mortality rate per 100 cases based upon experience with the disease in San Francisco. The increasing incidence of the disease in the older age groups has also been noted in many other cities in the United States.[6]

The present study was undertaken to determine the recent epidemiological phenomena of diphtheria in San Francisco and to analyze the cases from a clinical viewpoint in an effort to demonstrate some of the factors influencing the recognition and course of the disease in the individual patient.

MATERIALS AND METHODS

The present investigation covers the nine-year period from January 1942 through December 1950. Statistical material on reported cases of diphtheria in the state of California and in San Francisco county over that period was made available by the State of California Department of Public Health, Bureau of Communicable Disease Control, I. M. Stevens, morbidity statistician.

The patients included in the investigation were all hospitalized in the isolation division of the San Francisco Hospital during the years 1942 to 1950, inclusive. The criteria for inclusion required that the clinical diagnosis of diphtheria had been confirmed either by the isolation of Corynebacterium diphtheriae or, in a few instances, by the occurrence of neurological complication ascribable to the toxin of this organism. The postmortem observation of pathological changes typical of the acute disease process in the respiratory tract was also considered adequate evidence. These criteria account for a great part of the discrepancy between the number of cases reported for the county of San Francisco and the number presented in this study. For example, diphtheria might have been diagnosed on clinical grounds, diphtheria antitoxin used in treatment, and the case reported to the Department of Public Health as a case of diphtheria; yet if all cultures were subsequently reported negative for Corynebacterium diphtheriae, the case would be excluded from this study.

All culture material was immediately inoculated onto Loeffler medium and placed in a bacteriological incubator. Interpretation of the cultures was carried out in the laboratories of the department of public health of the City and County of San Francisco.

The criteria for the diagnosis of the various complications of diphtheria require special note. The presence of myocarditis was confirmed in every instance, either by electrocardiogram or postmortem examination. The criteria of electrocardiographic abnormality have been described in detail elsewhere.[3]

The diagnosis of neurological complications was based entirely on the clinical observation of sensory or motor changes in the areas served by the nerve groups involved.

Respiratory obstruction was considered, for statistical purposes, to exist in those cases in which tracheotomy was done or in which atelectasis was noted either clinically or postmortem. Minor degrees of respiratory obstruction associated with laryngeal diphtheria were classified in the present study merely as laryngeal involvement.

Antitoxin was given intravenously in almost all cases.

RESULTS

Epidemiological Observations

It will be noted in Table 1 that in the state of California as a whole the incidence of diphtheria declined in the years 1948, 1949, and 1950, while in San Francisco County it increased, and the proportion of cases in California which occurred in San Francisco County increased sharply. While not every patient with diphtheria in the county was hos-

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TABLE 1.—*Total Number of Cases of Diphtheria in California, in San Francisco County, and in San Francisco Hospital*

	1942	1943	1944	1945	1946	1947	1948	1949	1950
Total Cases in California	883	1,167	1,215	1,299	1,186	774	444	457	268
Total Cases in San Francisco County	29	41	20	54	53	45	92	82	48
Total Cases in San Francisco Hospital	20	22	6	28	32	44	56	43	22
Per cent of State Cases in San Francisco County	3.2	3.5	1.6	4.1	4.4	5.8	20.7	17.9	17.9

TABLE 2.—*Diphtheria Cases in California, 1942-1950, by Age Groups*

Year	0 - 14 Years		15 - 39 Years		40 Years and Older	
	Number	Per Cent of Total	Number	Per Cent of Total	Number	Per Cent of Total
1942	525	60.6%	222	25.6%	120	13.8%
1943	785	68.5	244	21.3	117	10.2
1944	830	70.0	268	22.6	88	7.4
1945	860	67.2	328	25.6	93	7.2
1946	776	67.0	288	24.9	94	8.1
1947	467	61.6	211	27.9	80	10.5
1948	209	48.0	126	29.0	100	23.0
1949	191	42.6	160	35.6	98	21.8
1950	107	40.4	87	33.0	70	26.6

Note: Only those cases in which the age was stated are included in this table.

pitalized at the San Francisco Hospital, the difference between the number of reported cases for the county and the number of patients recorded in Table 1 as having been in the San Francisco Hospital with diphtheria is accounted for, largely, by the criteria established for inclusion of cases in the present study.

Of the total of 273 patients (San Francisco Hospital, 1942-1950) included in the study 65 per cent were males and 35 per cent females. This ratio did not vary significantly when computed year by year. The mortality rate for males over the nine-year period was 20.2 per cent and for females 17.8 per cent. In the total group of 273 cases, there were only eight Negroes and three Orientals, distributed at random over the nine-year period.

Data on cases of diphtheria in California, arranged according to the age of the patient, are presented in Table 2. Only those cases in which the age was given in the report to the California State Department of Public Health are included. There was a significant increase in the incidence of diphtheria in the group of persons aged 40 years and older, and a steady decline through the nine-year period in the incidence of the disease in the youngest age group comprising children from birth to 14 years of age. In the age group 15 to 39 years there was only a slight increase over the course of the nine-year period. In a similar analysis of diphtheria cases in San Francisco County, data were included to cover a longer span of time (Table 3) and the increasing incidence of diphtheria in the older age groups was even more striking.

In the present series of 273 cases, eight patients

TABLE 3.—*Increasing Incidence of Diphtheria in Patients Over 30 Years of Age in San Francisco*

Year	Per Cent of Total Cases	Year	Per Cent of Total Cases
1922	9	1944	35
1924	8	1946	57
1926	8	1948	69
1942	52	1950	54

Data for years 1922-1926 from J. C. Geiger, M.D., Bulletin, San Francisco Department of Public Health, October 27, 1947; for years 1942-1950 from California State Department of Public Health, Bureau of Disease Control.

gave a history of having had diphtheria previously. One of them, who gave a history of diphtheria as a child, had two separate attacks of typical diphtheritic pharyngitis in the course of a year during the present study.

In the last year of the study the Schick test was performed in a number of patients on admission one hour before antitoxin was administered. The rapid local fixation of the toxin of Corynebacterium diphtheriae makes such testing possible, and the results are little influenced by the subsequent introduction of antitoxin.[8] In 13 such tests on patients included in this investigation, the result was positive in ten cases and negative in three.

An attempt was made to determine the magnitude of the burden placed upon the hospital by cases of diphtheria. The average period of hospitalization for the patients who died was fairly constant at about ten days for the nine-year period; for patients who recovered, it ranged between 25 and 48 hospital days, with a tendency in recent years to longer

hospitalization. The total hospital time for patients who recovered averaged 1,063 days per year over the nine-year period.

CLINICAL FEATURES OF DIPHTHERIA

Location of Infection

Diphtheria may involve any part of the respiratory tract, other mucous membranes, or the skin. All but one patient in this series had diphtheritic infection of the respiratory tract (Table 4). One patient had cutaneous infection as the only manifestation and nine others had skin involvement in addition to a lesion of the respiratory system. Of the 273 patients, 173 (63.4 per cent) had a diphtheritic lesion limited to one anatomical area; 100 (36.6 per cent) had lesions in more than one area. While laryngeal diphtheria was present in 75 patients, only 12 had lesions of the larynx in the absence of pharyngeal diphtheria. In 94.1 per cent of all patients, pharyngeal diphtheria was present.

Symptoms and Signs

The systemic symptoms of early diphtheria were generally mild and insidious in onset. Soreness of the throat was rarely severe at the beginning, but increased gradually to a maximum after several days and often persisted for many days. Headache, muscular aching, malaise, and prostration were not usually severe in the early stages of infection. Fever was often low-grade or absent. Chilliness was noted frequently, but frank chills were uncommon.

The local lesion in the pharynx in its typical form consisted of a grayish, tenacious pseudomembrane, confluent over areas involved, and often extending beyond the tonsillar fossa to the posterior pharyngeal wall. Extension to the soft palate and uvula was frequently observed. Early pseudomembranes appeared translucent and merged almost imperceptibly into the surrounding mucous membrane. Later lesions appeared denser and became more sharply demarcated. Edema of the tissues was often prominent. Erythema was commonly limited to a narrow area around the pseudomembrane. Atypical lesions were common and included follicular or patchy pseudomembranes, pseudomembranes variously colored from greenish to black, complete absence of pseudomembrane, and diffuse erythema of mucous membranes.

The manifestations of laryngeal diphtheria were similar to those of other forms of laryngitis. Croupy cough, hoarseness, stridor, and obstructive dyspnea were usually present. Complete aphonia was common. When laryngeal diphtheria was suspected and there was no pharyngeal involvement, visualization of the larynx was carried out to confirm the diagnosis.

Anterior nasal diphtheria was characterized by persistent nasal discharge, often blood-tinged and frequently unilateral. Pseudomembrane was usually visible after removal of secretions.

Cutaneous diphtheria was observed as an ulcerative lesion which did not necessarily have pathognomonic features. Early lesions often consisted of flat bullae partly filled with pus, surrounded by an area of erythema. Late ulcers were only occasionally covered by pseudomembrane and were clinically indistinguishable from other indolent ulcers. Anesthesia of the base of the ulcer occurred in several patients. This symptom was of great diagnostic aid.

Complications

Myocarditis, obstruction of the respiratory tract, and neuritis were the most commonly noted complications of diphtheria (Table 5). Myocarditis and neuritis occurred more frequently in the older age groups, while respiratory obstruction was more common in children. In addition, pneumonia occurred in five patients, nephritis in five, embolism of the femoral artery in one, and general hemorrhagic tendency in one.

Myocarditis occurred in 100 patients (36.6 per cent). The average time of appearance after the onset of infection was 9.8 days; the range was from two to 47 days. It appeared on the average earlier (7.2 days) in patients who died than in those who recovered (11.4 days). In many instances of myocarditis of mild degree, electrocardiographic abnormalities were the only manifestation. In more severe cases anginal pain, abdominal pain, syncope, pallor, vomiting, hypotension, arrhythmia of many varieties, deterioration in quality of the apical first heart sound, gallop rhythm, and murmur were noted. Abnormalities as observed electrocardiographically often lasted weeks or months but appeared to be permanent in only one patient. Of 100 patients in whom myocarditis was diagnosed, 36 died.

Severe obstruction of the respiratory tract occurred only in patients who had involvement of the larynx, sometimes in association with diphtheria of the trachea and bronchi. Of 40 patients with severe degrees of obstruction, 26 (65 per cent) died. Atelectasis and pneumonia were also considered to be of obstructive origin.

Neuritis was diagnosed in 44 patients, of whom six (13.6 per cent) died (Table 6). In 16 patients,

TABLE 4.—*Mortality Rates Related to Location of Diphtheritic Lesion*

Location	Total Cases	Deaths	Per Cent Mortality	
N	2	0	0.0	Single Location 5.7
P	158	8	5.0	
L	12	2	16.7	
C	1	0	0.0	
NP	29	5	17.2	Multiple Location 42.0
PL	43	23	53.5	
LT	1	1	100.0	
PC	7	1	14.3	
NPL	13	6	46.2	
PLT	2	2	100.0	
NPC	1	0	0.0	
NPLT	3	3	100.0	
NPLC	1	1	100.0	
	273	52	19.1	

Legend: N—Nasal
P—Pharyngeal
L—Laryngeal
C—Cutaneous
T—Tracheobronchial

TABLE 5.—*Incidence of Complications and Deaths Due to Diphtheria According to Age*

Age Group	Number of Patients	Patients with Complications	Total Complications	Patients with Myocarditis	Patients with Obstruction	Patients with Neuritis	Patients with other Complications	Deaths
0 - 14 Years	85 (31.1%)	36 (42.4%)	44	20 (23.5%)	20 (23.5%)	2 (2.4%)	2 (2.4%)	15 (17.5%)
15 - 39 Years	65 (23.8%)	28 (43.1%)	35	20 (30.8%)	5 (7.7%)	8 (9.6%)	2 (3.0%)	5 (7.7%)
40+ Years	123 (54.9%)	77 (62.6%)	116	60 (48.8%)	17 (13.8%)	33 (26.8%)	6 (7.2%)	33 (26.8%)
All Ages	273 (100.0%)	141 (51.6%)	195	100 (36.6%)	42 (15.8%)	43 (15.8%)	10 (3.7%)	53 (19.4%)

Percentages indicate incidence in age group.

cranial nerves as well as nerves of the extremities were involved. Twelve patients had neuritis only in the extremities. Four had glossopharyngeal neuritis only, and in two patients the vagus alone was involved. In ten patients who did not have neuritis of the extremities, the ninth and tenth cranial nerves were both involved. Of the six patients with neuritis who died, four had involvement of the vagus nerve. Intercostal and diaphragmatic paralysis was present in the other two. In cases in which glossopharyngeal paralysis occurred, a nasal quality to the voice and regurgitation of fluids through the nose often preceded visible diminution of palatal movement. Vagal involvement was manifested by dysphagia, accumulation of secretions, and aphonia. Neuritis of the extremities was often heralded by paresthesias and numbness, followed by diminution of deep reflexes and loss of motor power in a symmetrical fashion. An increase in the spinal fluid protein content, without pleocytosis, was common. Recovery from postdiphtheritic neuritis was often very slow but was always complete.

Glomerulonephritis was diagnosed in five patients, four of whom died. In the patient who lived, chronic glomerulonephritis with hypertension persisted. It was not certain that this lesion was diphtheritic in origin. Embolism of the femoral artery was observed in one patient and was presumed to result from a mural thrombus complicating diphtheritic myocarditis.

Treatment and Results

With rare exceptions diphtheria antitoxin was administered within a few hours after the patient was admitted to the hospital. Skin and conjunctival tests for sensitivity to horse serum were invariably performed. Antitoxin was administered intravenously, usually diluted in an infusion of 5 per cent glucose solution or normal saline solution, to all but a few patients. Those patients who had positive reaction to sensitivity tests received all or part of the antitoxin intramuscularly. Intramuscular injection was also used in a few cases in which the disease was mild and in an early stage. The dose of antitoxin ranged from 10,000 to 100,000 units; the most frequently used was 40,000 units. The size of dose depended upon the location of the lesion, whether one or more anatomical areas were involved, and the duration of the disease. The weight of the patient was given little consideration in determining the amount, and the entire dose of antitoxin was given at one time. Serum reactions occurred in 28 patients (10.5 per cent). They occurred as early as the day of treatment and as late as the 26th day after treatment; the average was 8.8 days after antitoxin was administered. Reaction was not fatal in any case.

In the latter years of the period covered by this study, most patients received penicillin intramuscularly for one week or more. In no instance did penicillin appear to affect the course of the diphtheria or the incidence of complications. As was previously reported,[2] however, there was earlier disappearance of Corynebacterium diphtheriae from the respiratory tract in those cases in which penicillin was given.

Tracheotomy for the relief of respiratory obstruction was done in 22 cases. Ten of the patients died. Suction frequently was used for relief of obstruction, and oxygen was administered when it was deemed necessary. Myocarditis was treated by complete rest, and, if associated with clinical manifestations, by oxygen and sedation. Hypertonic glucose solutions appeared to have little effect. Patients with severe hypotension were given ephedrine and infusions of plasma. Digitalis was used only in those cases in which myocarditis was associated with auricular fibrillation or flutter with rapid ventricular rate.

All patients were maintained at bed rest for three weeks or until electrocardiographic tracings became normal. Activity was thereafter gradually increased until the patient was able to care for himself at home.

The longer the time between the onset of illness and the administration of antitoxin, the greater the incidence of complications and the higher the mortality rate (Table 7). In the cases in which no com-

TABLE 6.—*Incidence and Time of Onset of Post-Diphtheritic Neuritis*

Nerve	Patients	Interval Between Onset of Diphtheria and Onset of Neuritis — Average (in days)	Range (in days)
Extremities	28	48.0	21-91
Ninth cranial	21	31.9	6-53
Tenth cranial	22	33.9	10-62
Other cranial	4	—	12-60

TABLE 7.—*Mortality Rate in Relation to Interval Between Onset of Disease and Injection of Antitoxin*

Day Treatment Started	No. of Cases	No. of Fatal Cases	Mortality Rate (per cent)
1	9	0	0.0
2	26	1	4.0
3	31	5	16.1
4	46	8	17.6
5	40	8	20.0
6	28	6	21.4
After 6 days	67	20	29.9

plications developed, the average duration of illness before treatment was 4.4 days. For patients who had complications and recovered, the interval between onset and injection of antitoxin averaged 5.7 days; for those who died, 6.6 days. Twenty-five per cent of patients in this series did not receive antitoxin until seven or more days after onset of disease.

In the group of cases in which diphtheria was localized to one anatomical area the mortality rate was 5.7 per cent; in the group in which lesions involved two or more areas, it was 37 per cent (Table 7). The mortality rate was highest in the oldest age group and lowest in the middle age group (Table 5). The deaths among children were largely attributable to respiratory obstruction, which was of relatively high incidence in this age group. In the cases in which the patients had obstruction and recovered, the average interval between onset of disease and injection of antitoxin was 3.4 days; in the cases in which patients died of obstruction it was 6.8 days.

DISCUSSION

It is evident from the data presented that the incidence of diphtheria, while it has decreased in recent years in the state as a whole, is still significant and warrants the continued attention of physicians.

Although the data in this report indicate that in recent years an increasing proportion of the total number of cases in the state occurred in San Francisco County, this may be in some measure misleading. While the reported relative increase in San Francisco cannot be ascribed to shifts in concentration of population (for the population of San Francisco grew considerably less rapidly in the last ten years than did that of the state as a whole), it is conceivable that there was greater frequency of recognition of diphtheria in San Francisco than elsewhere in the state, rather than concentration of occurrence of the disease there.

The traditional statement that diphtheria has no predilection for persons of any one race[5] is not borne out in the present study. The number of cases of the disease in Negro and Oriental patients was low in relation to the proportion of persons of those races in the total population of the county. Of the patients in the present series, 2.9 per cent were Negroes and 1.1 per cent were Chinese, whereas almost 7 per cent of the residents of the county are Negroes and about 2.5 per cent are Chinese. Likewise, the larger proportion of males with the disease seems of interest and is not readily explained. The relative increase in incidence in adults, and especially in adults over 40 years of age, seems most important. The explanation for this probably is that in the widespread immunization programs, the younger persons are protected while the older persons are not. Most adults have not been artificially immunized, and it is probable that development of natural immunity has decreased in recent years because of less exposure to the organism. In Schick-testing of elderly adults a high rate of susceptibility was noted.[1] The administration of toxoids to adults entails increased risk of serious reaction, unless special techniques and precautions are used.[1] The increased incidence of complications in the older age groups may explain the increase in average length of hospital stay observed in the present study. The higher mortality rate from the disease in older persons puts further stress on the importance of the relative increase in incidence in the higher age groups.

The present investigation demonstrated that clinical infection with Corynebacterium diphtheriae is not necessarily a good stimulus to the production of active immunity and that recurrence is possible. This would seem to indicate Schick testing for convalescent patients and the giving of toxoid if there is positive reaction to the test.

It is apparent that the prolonged stay in the hospital requisite for patients with diphtheria represents a real burden on the hospital facilities of a community. More widespread utilization of the relatively simple means of prevention of the disease would offer an answer to this purely socio-economic feature of diphtheria.

The outcome of diphtheritic infection depends primarily on the amount of toxin fixed in the tissues. This, in turn, depends on the location of the lesion, extent of involvement, duration of infection before antitoxin is given, and resistance of the patient. Since diphtheria toxin is fixed in the tissues so rapidly and firmly that only a small part can be neutralized by antitoxin, it is vital that unfixed toxin be neutralized at the earliest possible moment by the introduction of antitoxin. This necessitates early diagnosis and treatment based on suspicion. Since diphtheria involves the pharynx in 95 per cent of patients, recognition of the lesion in this readily visible area will permit presumptive diagnosis in almost all cases. Because the incidence of fatalities and complications rises sharply with each day of delay, antitoxin must be administered at once in all cases in which diphtheria cannot be excluded by careful examination of the upper respiratory tract. Bacteriological diagnosis before treatment is a luxury that carries with it the risk of fatal delay, although confirmation of the diagnosis by culture must be sought in all cases.

Atypical features of the disease are common and must be kept constantly in mind. Although laryngeal diphtheria is usually associated with pharyn-

geal diphtheria, laryngoscopy should be carried out in all cases of laryngitis in which diphtheria cannot readily be excluded. Nasal and cutaneous diphtheria may persist for weeks or months. Absorption of toxin is relatively slight in such cases but may result eventually in myocarditis or neuritis. Cultures should be made in all cases in which persistent nasal discharge or indolent skin ulcers are present, and treatment should be started as soon as possible if Corynebacterium diphtheriae is present.

Complications are the cause of death from diphtheria. Myocarditis and respiratory obstruction commonly coexist, and death results from their additive effect. The earlier the appearance of myocarditis, the greater the probability the patient will die. Neuritis of the tenth cranial nerve may cause atelectasis and pneumonia due to aspiration of secretions, and these complications must be dealt with by frequent suction of the respiratory tract and lowering of the patient's head. Often it is necessary to feed the patient by tube or intravenously. If there is paralysis of the muscles of respiration, a mechanical respirator must be used.

Diphtheria antitoxin is the single important agent in the treatment of this disease. Because of the necessity for immediate neutralization of circulating toxin, the intravenous route appears to be the one of choice in most instances. Exact dosage requirements cannot be stated. They vary between 20,000 and 100,000 units, depending upon the site, the extent and the duration of infection. The entire amount should be given at one time. Under-dosage and repeated small doses are to be condemned. Serious serum reactions are rare, although serum sickness constitutes an annoying problem.

Penicillin therapy, in conjunction with antitoxin, contributes little to the successful outcome of a case of diphtheria.[2] Furthermore, the administration of penicillin in no way modifies the requirement for antitoxin.

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